URVEY

ol/l)

SD	Significance (by χ^2 test)
5.6	
7.6	
	P < 0.01 (2 vs 3)
8.5	
8.8	P < 0.01 (from 1)

levels of circulating oestradiol

rum alkaline phatase (King-Armstrong units)	Average % fat
9.0 ± 0.5	33.7
1.5 ± 0.9	28.2
P < 0.05	P < 0.01

l decrease in the level of in the group with levels of 100 pmol./l. This decrease to decreased bone turnover As might be expected from in the preceding section, gh circulating levels of es- ore obese, with an average body fat.

ar calcium-creatinine ratio relationship between fast- estradiol levels. The lower ting estrogen, the greater is possible, therefore, that estrogen in some way de- g of calcium.

threshold for phosphorus circulating estradiol levels plex than that obtained for

trogen production may be determining bone loss in 1.

that endogenous rough increasing ng findings is that

there is a significant estradiol level in the serum of oophorectomized women as long as four years after oophorectomy. And again, it has been confirmed that obese women have significantly higher estradiol levels than non-obese.

As time goes on, the prevention of incapacitating osteoporosis seems to be the major indication for postmenopausal estrogen replacement therapy. The prevention of cardiovascular disease seems to be less and less discussed. The Framingham study (OGS *32:* 235, 1977) reported a correlation between the menopause and cardiovascular disease but the only *significant* correlation, in my opinion, was the increased risk of cardiovascular disease in patients with a surgical menopause prior to the age of 40 years. This rather tenuous evidence for protection by estrogen against arteriosclerotic vascular diseases, has apparently been over-ridden by the convincing evidence that estrogen does predispose to thrombo-embolic phenomena and hypertension, thus increasing the danger of coronary artery disease and strokes. When one throws into the hopper the increased risk of gall bladder disease, recently discussed in the Survey and again in the New England Journal of Medicine, May 26, 1977 (*296:* 1185, 1977), the enthusiasm for estrogen forever is somewhat dampened even without considering the possibility of a predisposition to endometrial carcinoma.

The synergism between estrogen and cigarette smoking on the increased risk of both cardiovascular complications (OGS *32:* 245, 1977) and osteoporosis (OGS *31:* 808, 1976) is apparently another important aspect in deciding who and when to treat. Nicotine promotes vascular constriction and estrogen increases coagulability, and these two make a very poor combination. In the long run, your patients who have evidence, by either serum estradiol or vaginal smears, of a true estrogen deficiency, are the ones who should be considered for replacement estrogen therapy. They should not be treated if they are thin and heavy smokers. The point is made also that one does not need a high dose of estrogen. Small doses are apparently adequate to maintain calcium homeostasis. However, if you can persuade your patients to (1) stop smoking, (2) drink two or three glasses of milk a day, (3) maintain their weight at a little above optimum and (4) carry on a regular exercise program, you can cut down on the check examinations required for patients on estrogens.—Ed.)

ESTROGENS AND ENDOMETRIAL CARCINOMA

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A group of 205 women with endometrial carcinoma was matched for age, parity and year of operation with a group of 205 women who had had hysterectomies for benign disease.

Fifty-five of the 205 patients with cancer and 31 of the 205 controls had used some form of estrogen-containing medication. The majority had used conjugated estrogens yielding an RR (relative risk) of 3.1. All categories of systemic estrogens were associated with elevated RR's including intramuscular estrone and other types of estrogen tablets—primarily stilbestrol and ethinyl estradiol. Grouping all systemic estrogens yields an RR of 2.6. There was no evidence of

increased risk associated with vaginal estrogenic preparations (creams, estrogen-impregnated pessaries) or oral contraceptives although the latter were not used frequently enough to be evaluated adequately. Matched pairs analysis yielded identical results.

The effects of length of use and strength of tablets usually used were investigated for those using conjugated estrogens. The RR increased with increasing duration of use, with no appreciable increase in risk apparent for those using the medication for less than five years. Those using it for five to nine years had a fourfold increase in risk, and those using it for ten years or more had a risk 11½ times that of nonusers. Those usually using the 1.25 tablet had a risk markedly above that for users of the 0.3 or 0.625 mg. tablets. The estimate of RR was lower for users of the 0.6 mg. tablet than for those using the 0.3 mg. dose, but the estimates were variable because of the small numbers involved. When attention was restricted to those using the drug for more than five years, the RR for users of the 0.3 mg. tablet was identical to that for those using the 0.625 mg. tablet. The associations with duration of use and strength of tablet do not confound each other, as the estimates of RR remained unchanged when control for the other variable was added.

The anticipated differences between study patients and controls in obesity, hypertension and history of diabetes were present. None of the patients with a history of diabetes were estrogen users. Control for weight and systolic blood pressure did not diminish the associations with hormone use. In fact, simultaneous control for both of these variables increased the RR for systemic estrogens to 3.6.

For 184 of the study patients and 179 of the controls there was clear and specific information recorded on whether there had been any abnormal uterine bleeding in the year prior to hysterectomy. As anticipated, the study group had a positive history much more frequently than the controls (85 versus 33 per cent). The relative risk for use of systemic estrogens was slightly higher among those with no history of abnormal bleeding than it was for those with such a history (3.4 versus 1.8). However, with the numbers involved, these two estimates were not significantly different from each other.

Most endometrial cancers had been carefully staged and graded. The percent distribution by stage was remarkably similar for users and nonusers of systemic estrogens. There was some evidence of a difference in pathologic grading between users and nonusers, there being a higher proportion of users in the lowest grade and a lesser proportion in the highest. However, the differences were not statistically significant, and there was no evidence of a linear trend in the differences between the users and nonusers.

(This is one of two recent reports which greatly strengthen the evidence for an association between exogenous estrogen therapy and endometrial carcinoma. Since the articles by Smith et al. and Ziel and Finkle (OGS *31:* 34, 1976) demonstrated an apparent 7 to 8-fold increase in the risk of developing endometrial carcinoma among estrogen users, the discussion has been hot and heavy. The criticisms of these earlier studies have been directed at the inappropriateness of the control groups and the lack of careful pathologic evaluation. This report by Gray et al. and the excellent article by McDonald and his co-workers from the Mayo Clinic (Amer. J. Obstet Gynecol *127:* 572, 1977) seem to answer these objections quite adequately.

Although it is difficult to choose an entirely satisfactory control group in a retrospective study of such a complex problem, both of these reports have done quite well. The possibility that the true incidence of endometrial cancer has been underestimated in the control population has been suggested by some critics. However, by using age-matched patients undergoing hysterectomy for benign indications, Dr. Gray eliminates the possibility that any patients in the control group are silently harboring undiagnosed endometrial cancer, since the uterus was examined in all cases. In general, it seems unlikely that any fault with the

control groups is of great significance, since each of the studies thus far has used somewhat different controls, but have arrived at the same conclusion.

The lack of careful pathologic evaluation in the previous reports has been a serious fault, but this has been corrected in these most recent series. Dr. Christopherson and Dr. Dockerty are well recognized gynecologic pathologists, and only cases which they felt represented invasive carcinoma of the endometrium have been included in these studies. Patients were grouped according to stage, and other pathologic factors such as degree of tumor differentiation and depth of myometrial penetration. Like Mack et al. (New Eng. J. Med. *294:* 1262, 1976), the Mayo Clinic series found that estrogen users had the greatest risk of developing Stage I, well-differentiated, minimally invasive cancer. The group from Louisville did not find an increased incidence of Stage I tumors, but the 88 per cent incidence of Stage I carcinoma among the control patients is somewhat higher than commonly reported. On the other hand, every series has reported patients in the estrogen-treated group with poorly differentiated, deeply invasive, advanced endometrial carcinoma, so that it cannot be said that estrogens serve a protective effect or assure an early diagnosis.

These studies have also confirmed the concept that higher doses, prolonged therapy and continuous administration all lead to an increased risk. It is not yet known if there is a minimum level of dose or length of exposure below which there is essentially no increased risk for developing endometrial carcinoma. There is also no reason to believe that one estrogen preparation is preferable to another, although this has not been adequately investigated at the present time.

I am still using estrogens in those patients who benefit from it and it may be that the lower risk ratios reported by these two recent series (3.1 and 2.3) are the result of an attempt to follow the rule of lowest dose for the shortest time.—HWJ, III)

COLPOSCOPY AND THE MANAGEMENT OF CERVICAL INTRAEPITHELIAL NEOPLASIA

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The accuracy of the colposcopically directed punch biopsy and its value in the management of cervical intraepithelial neoplasia (C.I.N.) was evaluated among 272 consecutive patients with abnormal Pap smears who were followed in a cervical dysplasia clinic (Bellevue Hospital, New York University Medical Center).

Patients who had colposcopic findings of mild to moderate dysplasia, in whom the entire lesion was visualized and the endocervical curettings were negative, were treated by cryocauterization alone.

Cone biopsy was performed under any of the following circumstances: if the entire squamocolumnar junction was not visualized, if the colposcopically abnormal areas extended up the endocervical canal, out of view, or if the endocervical curettings contained dysplastic epithelium.

Cone biopsy was also indicated when a negative, or minimally abnormal, colposcopic exami-